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HEALTH ASPECTS OF ENVIRONMENTAL TOBACCO SMOKE:

AN EVALUATION OF THE SCIENTIFIC LITERATURE

Submission to the Health Care Committee of the NH&MRC

Report prepared by an independent group convened by

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PREFACE

In February 1994 the National Health and Medical Research Council called for expressions of interest to assist the Health Care Committee Working Party in its revision of the 1986 Report "Effects of Passive Smoking on Health". A specific brief was to "examine whether a link exists between passive smoking and disease in adults and children."

The present report was prepared at the request of the Tobacco Institute of Australia. Its contents represent a rigorous, objective evaluation of the scientific literature on this subject by a group of scientists convened by Dr Julian Lee.

The financial support necessary to undertake this task has been provided by the Institute. Editorial independence was guaranteed and has been preserved throughout. The conclusions expressed in this document are those of the Working Group acting as an independent body.

Principal authors of material in Sections 3 and 4 are as follows:

3.1 -3.4	Childhood Health Outcomes: JE, JP, MF
3.5	SIDS: PC
4.1	Respiratory Illness in Adulthood: DM
4.2	Lung Cancer in Adulthood: WD, KM
4.3	Heart Disease in Adulthood: MM, KM

The entire document was read and supported by everyone in the Group.

CONTENTS

EXECUTIVE SUMMARY

I. GOAL

This report summarises our scientific assessment of possible associations between exposure to environmental tobacco smoke (ETS) and the following health effects:

- upper and lower respiratory illnesses, impairment of lung function, asthma and SIDS in children
- lung cancer, heart disease, exacerbation of asthma and impairment of lung function in adults

The report is set out as follows:

1: Introduction.
2: Criteria for establishing a causal relationship between a potentially harmful agent and a health outcome in a population and discussion of the criteria by which the quality of epidemiological studies should be assessed.
3: Assessment of whether exposure to ETS is significantly associated with adverse health effects in children
4: Assessment of whether exposure to ETS is significantly associated with adverse health effects in adults.

This approach reflects our belief that scientific proof should be based on a set of agreed and well defined criteria, and that any potential causal relationship should be evaluated accordingly. These criteria include facets of logic, biological plausibility, strength and consistency of the statistical association, and its robustness to the many possible sources of bias and confounding. This is not to imply that policy development must be based only on absolute proof.

Because of their commonality to all of the epidemiological and experimental studies referred to in this report, problems of quality and their potential impact are discussed prior to detailed evaluation of the relevant literature.

II. BASIS OF OUR OPINION

Our opinion has been formed on the basis of professional experience and a critical evaluation of relevant published papers and reviews of this literature. We believe that the literature which we have reviewed comprises the main papers in the areas of interest. This material has been drawn from major databases (including Medline and Cancerlink) and papers referred to in published reviews.

III. SUMMARY OF CONCLUSIONS

(i) HEALTH EFFECTS IN CHILDREN

The effects of ETS on the health of infants and children are difficult to separate from the many effects of confounding factors such as socioeconomic status, genetic disposition, family history of illness, breast feeding and maternal smoking during pregnancy. The last factor is rarely considered (except in relation to Sudden Infant Death Syndrome) and is likely to be confounded with maternal smoking after pregnancy.

Generally speaking, the mechanisms and causes of illnesses in children which may be associated with ETS are unknown.

Lower respiratory illness

Exposure to ETS is associated with an increased risk of lower respiratory tract infections in infants. There is a weak association between exposure to ETS in infancy and subsequent likelihood of developing asthma. After adjustment for chest infections in infancy the risk is reduced. Other confounders have been documented to be important, hence causation has not been demonstrated. It is unclear whether the important factor is exposure to ETS in infancy *per se* or active smoking during pregnancy, which is associated with lower birthweight and narrower airway calibre. The situation with respect to older children is unresolved.

Lung function

The literature on the effects of ETS on lung function in children is inconsistent, with the majority of studies showing only small changes, if any. Confounding factors such as family history of illness, early respiratory illness and low birthweight appear to play an important role. The clinical significance of any observed small changes is unknown.

Upper respiratory illness

Exposure to ETS is associated with only a small increase in risk for upper respiratory tract infection in children; this is not the only risk factor, and probably is not the most important. Other risk factors, such as day-care attendance and crowded living conditions, appear more important. Overall, the literature reported inconsistent results, and little in the way of discussion of biological mechanisms for any association with ETS.

Sudden Infant Death Syndrome (SIDS)

There are many risk factors with elevated relative risk for SIDS. The most prominent are: prone sleeping position, low birthweight, maternal smoking during pregnancy and low socioeconomic status of the mother. The mechanisms and causes of SIDS are unknown. A causal relationship has not been established between SIDS and either maternal smoking during pregnancy or after the birth.

(i) HEALTH EFFECTS IN ADULTS

Respiratory Effects

Acute effects on lung function:

There is no evidence that exposure to high levels of ETS for periods of up to 2 hours causes a detectable change in airway function in healthy subjects. Significant decreases in airway function have been observed in some asthmatics with moderate or severe bronchial hyper-responsiveness, but clinically significant bronchospasm appears to be a rare event. A dose response relationship has not been documented conclusively and there are some contradictory data. The effects are transient and can be reversed promptly or prevented by inhalation of a

bronchodilator. The possible protective effect of adequate prophylactic medication has not been investigated systematically.

Effects of chronic exposure:

Clinically significant effects of long-term exposure to ETS on pulmonary function in healthy adults have not been documented. Asthma is associated with impaired lung function and an accelerated decline in airway function with time. Active smoking has little effect on this rate of decline but it is possible that those asthmatics who were affected managed to cease smoking. The available data do not support the hypothesis that asthmatics are especially susceptible to long-term respiratory effects of ETS.

Lung Cancer

To assess the possible association between surrogate measures of ETS exposure and risk of lung cancer, more than 30 individual epidemiological studies have been reviewed. Several reviews and meta-analyses of the individual studies have also been addressed. Our conclusions, based on a synthesis of these various sources, appear below.

Spousal exposure

There is an overall positive association between spousal smoking and lung cancer, but this association is not strong. Current combined estimates of relative risk typically range from 1.0 to 1.4. Although this is unlikely to have arisen by chance alone, there is considerable variation in the quality of studies and we cannot exclude the possibility that various forms of bias and confounding may explain the observed increases in relative risk. Moreover, the variability between study estimates, especially on a regional basis, indicates that representativeness must be considered before drawing any conclusions about a particular population.

Workplace exposure

Overall, there was no significant increase in relative risks for lung cancer in males or females. The exposure-response relationships from both sources (spouse and workplace) are equivocal. The epidemiological evidence indicates that exposure to ETS in childhood is not associated with an overall increase in relative risk for lung cancer.

Based on specified criteria for establishing causality and on the available data, we cannot conclude that exposure to ETS, either in the home or at work, or in childhood, causes lung cancer.

Heart Disease

About half of the 14 epidemiological studies of ETS report statistically significant increased relative risks for heart disease, but these are generally small.

A consistent exposure-response relationship has not been established and there remain concerns about study quality, particularly the impact of bias and poor control of confounders.

Compared with identified risk factors for heart disease, the association between ETS and heart disease, based on both epidemiological and biological evidence is weak.

There is evidence that exposure to ETS may increase short-term ischaemic stress in people with pre-existing coronary heart disease. Healthy persons are not generally affected.

At this stage neither the epidemiological nor the biological data support a causal relationship between ETS exposure and heart disease.

1. INTRODUCTION

Active cigarette smoking is injurious to health. Chronic lung disease (irreversible airway narrowing and emphysema) and lung cancer have the strongest associations. Approximately 15% of moderate to heavy smokers will develop disabling airflow limitation and a smaller proportion will develop lung cancer. There is also an increased risk of mortality from coronary artery disease among active smokers. Based on the assumption that there might be no safe level of exposure to tobacco smoke, and an extrapolation from the data regarding active smoking, concerns have been raised that passive smoking might produce qualitatively similar adverse health effects.

Infants and individuals with pre-existing disease have been regarded as groups who might be particularly susceptible to adverse effects from environmental tobacco smoke.

Involuntary ("passive") smokers inhale environmental tobacco smoke (ETS) which consists of sidestream smoke (SS, smoke emitted from the tip of a cigarette) and exhaled mainstream smoke (EMS). There are differences between mainstream smoke (MS) and ETS in the chemical composition and size of their particulate matter. It is uncertain which components of smoke are responsible for damage to the airways and lung parenchyma and it is not known, on a dose for dose basis, whether ETS is less, equally, or more likely than MS to lead to lung damage (Fielding & Phenow, 1988). There is some evidence that SS is more carcinogenic than MS (Surgeon General's Report, 1986) but it should be emphasised that active smokers are also exposed to high concentrations of SS.

Nonsmokers may be exposed to ETS at home, in the workplace, in public places and in recreational places. The amount of ETS indoors depends upon many factors including the size of the room, the number of smokers, the intensity and proximity of smoking by smokers, the type of cigarette smoked, and the ventilation or rate of air exchange (Fielding & Phenow, 1988).

In addition, the "dose" of ETS depends on the amount of air inhaled in a given time, which increases with exertion. Methods of estimating exposure to ETS include questionnaires, counts of respirable particles, atmospheric nicotine levels, carbon monoxide analysis of the air, urinary or salivary cotinine levels (a by-

product of nicotine metabolism which, to some extent, correlates with current exposure), and measurement of carboxyhaemoglobin in the blood (a measure of carbon monoxide inhalation) (Fielding & Phenow, 1988; Seppanen, 1977).

In 1986 the NH&MRC reviewed the scientific literature related to passive smoking and health effects and published its findings. The Council concluded that there was strong evidence that exposure in the first year of life was associated with an increased risk of lower respiratory tract illness. There was considerable information implicating parental smoking as a risk factor in middle ear effusions, reduced lung function, asthma attacks and Sudden Infant Death Syndrome (SIDS) but further study was needed to clarify whether these effects were due to exposure *in utero* from active smoking during pregnancy or subsequent passive smoking.

With respect to adults exposed to ETS, Council noted the evidence that it caused "acute irritant effects in the upper and, to a lesser extent, the lower respiratory tracts". "Asthmatics may suffer significant acute effects following exposure." There were insufficient data to conclude any important acute or long-term effects on lung function in healthy individuals. Council also concluded "it is.. prudent public health policy to infer an increased risk of lung cancer from passive smoking...despite limitations in the amount of data available". Concerning cardiovascular disease Council noted "there is very limited evidence available about the .. effects of passive smoking".

Since that Report appeared there have been numerous studies examining the potential health effects of ETS. The aim of the present review has been to determine whether any of these possible associations are now established and, if so, whether they can be regarded as causal.

2. METHODOLOGY

2.1 CRITERIA FOR ESTABLISHING A CAUSAL RELATIONSHIP

The major reviews of health effects associated with exposure to ETS (Surgeon General's Report (1986), NH&MRC Report (1986), NRC Report (1986), EPA Report (1992)) have all espoused some series of tests which should be evaluated in the establishment of a causal relationship.

The NH&MRC Report (1986) assesses a causal relationship as demonstrated through epidemiological studies by considering diversity of study designs and research methods, consistency of findings, interdisciplinary coherence, and biological and aetiological plausibility.

For qualitative hazard identification the EPA Report (1992) considers "weight of evidence" (p.1-2) which includes, in the evaluation of cancer, animal bioassays and genotoxicity studies, biological measurements of human uptake of tobacco smoke components, and epidemiological data on active and passive smoking. For noncancer outcomes, conclusions are based primarily on reviews of the available epidemiological studies.

For quantitative risk assessment, however, the EPA Report states (p.1-3) that "the usefulness of the studies usually depends on how closely the study population resembles nonsmoking segments of the general population". Hence the US studies alone are used for US assessment; the confidence in these risk assessments is stated to be "medium to high" (p.1-4).

All of the above reviews used a simplified and somewhat subjective version of the set of criteria proposed by Hill (1965). Despite the wide recognition that this set of criteria is not immutable, all of the issues identified by Hill are relevant to the relationships addressed in this paper. Subsequent discussions have enhanced rather than restricted the set of criteria (see, for example, Tweedie & Mengersen, 1994).

In the current report on the association between ETS and lung cancer, the evidence for causality is evaluated in the light of all nine of Hill's criteria. The

focus here is on establishing whether the relationship between an exposure and an outcome in a *population* is actually causal. Extra steps are needed to move from this to an assertion of causality in an *individual*.

Hill's criteria, adopted here, are as follows:

2.1.1 Strength

If the relative risk is 'large', there is less likelihood that other adequate explanations of the observed association exist. It is generally accepted, based on epidemiological studies, that a relative risk of at least 2 is required before the estimate can be confidently considered to be free of the influence of confounders and other sources of bias and selectivity. For example Layard (1994) states that "relative risks of less than 2 are generally considered to be weak." Cornfield is quoted by Wynder et al. (1987) as suggesting that a relative risk under 3.0 might be considered weak. Doll (1985) states "past experience suggests that confounding is seldom likely to be the explanation if the lower 95% confidence limit of the estimated relative risk is greater than 3." Mantel (1990) advocated that values below 2 should not be regarded as having established an association. The US EPA (1992) would not conclude that electro-magnetic radiation from power lines is harmful because relative risks of at least 3 were not achieved.

If relative risks greater than 2-3 were required, almost all of the studies of health effects of ETS in adults or children would not be considered to have established a significant and reliable association with any outcome.

Tests of strength of an association involve ruling out the possible influence of the following alternatives:

Chance: 'No other adequate explanation' implies that the relative risk is statistically significant; otherwise there is still an unsatisfactorily large probability that an observed increased relative risk is due to chance fluctuation or 'background causes'. In addition it is important to differentiate between a *statistically significant* and a *clinically important* relative risk.

Study Quality: Are the studies of sufficient quality in design, conduct and analysis such that biases cannot contribute to the observed association? Variable study quality is acknowledged as a problem in all major reviews of ETS. Section 2.2 is devoted to detailed discussion of this issue.

Confounders:

(i) Is there any detectable or reasonably inferred confounder that is so intimately linked with the exposure that it could explain the association?

(ii) Are there other factors which, while not entirely explaining the association, sufficiently influence the relative risk such that they must be considered in a study? If so, for a causal relationship to be established, it is essential to consider *representativeness* when extrapolating results to other populations.

2.1.2 Consistency

Has the association been observed repeatedly in different studies, and in different places, circumstances and times? Has it been observed using different study designs, such as prospective, retrospective, case-control and cohort studies?

2.1.3 Specificity

Is the association limited to the particular outcome? This is a difficult test to satisfy if the outcomes have more than one cause.

2.1.4 Temporality

Did the exposure precede the outcome? It is potentially invalid to establish an association based on current exposure if exposure has changed over time.

Day (1985, pp.16-17) argues that duration of exposure is more important than current exposure since the onset of disease may have a long latent period. He states (p.17) that "serious errors in interpretation can occur if the wrong time interval is used for assessing risk". Duration of exposure to ETS may be indicated by measures such as age or length of marriage, but has not always been well controlled.

2.1.5 Biological gradient

Is there an exposure-response relationship? It is not sufficient merely to view this 'by eye' when the overall relative risk is small. Statistical analysis is required to assess the effect of chance.

Testing a hypothesis of homogeneity of relative risk across exposure categories is different from actually developing a model to describe the exposure-response relationship. It is also important to differentiate between overall association and biological gradient; see Section 2.2.

The limitations of testing and modelling for biological gradients with ETS are due in part to the small number and inconsistent definition of exposure levels in the various studies. Hence any extrapolation from high to low doses must be viewed with caution, especially if the biological evidence is mixed (for discussion see Thomsen & Kjelsen, 1974).

It is crucial to establish the correct exposure-response relationship before attempting to predict the levels of risk for individuals at different levels of exposure, and hence in the assessment of attributable risk.

2.1.6 Plausibility

Is the proposed association explained by a biologically plausible mechanism?

The answer depends on the biological knowledge of the day. Different biological models can be constructed in retrospect to explain observed results; other evidence, such as clinical data, should support any postulated mechanism.

2.1.7 Coherence

The proposed relationship should not seriously conflict with generally known facts about the natural history and biology of the disease. This may be in the form of laboratory or clinical studies.

2.1.8 Experimental Evidence

If preventative action is taken because of an observed association, is the frequency of associated events reduced in subsequent studies? Is there no other possible cause of a particular outcome? Experimental studies on animals may provide some corroborative evidence.

2.1.9 Analogy

Is the proposed relationship analogous to some other accepted cause and effect? If so, we might accept weaker evidence, but it must be established that the

analogy is valid. In the case of ETS, for example, analogies with outcomes from active smoking must be on the basis that the chemical composition, exposure levels, inhalation patterns and associated outcomes (e.g. histological type of lung cancer) from the two types of smoke are the same.

On the application of these tests Hill (1965) stated "On scientific grounds the evidence is there to be judged on its merits and the judgement should be utterly independent of what hangs on it. It's another question entirely to ask what is involved in the decision."

2.2. STUDY QUALITY

There is considerable variation in the quality of the individual epidemiological studies relevant to this document, in terms of their size, design, execution and analysis. All major reviews of the health effects of ETS have addressed this issue to some extent. The EPA Report (1992), for instance, categorises studies of lung cancer into 'quality tiers' which are described as a measure of a study's "utility for investigating a potential association between ETS and lung cancer" (p.5-14). Of the 29 studies of spousal smoking exposure considered in the EPA Report, only five are categorised in the top tier and an equal number appear in the lowest tier; the latter are purported to be of such poor quality that they should not be included in any overall assessment.

There is ongoing debate about the validity of categorising studies according to quantitative scores, and about the scoring methods themselves. In the absence of an agreed method, our approach has been to detail the possible sources of poor quality and to assess whether any one of these could explain the observed associations. While an individual source of poor quality may not be identified, the accumulation of these sources may explain the observed association.

One approach is to consider each study separately and make a judgement about the validity of its conclusions. Often this is not feasible since necessary methodological information is not provided. It would be naive to assume that because a study has been reported in a peer-reviewed journal, all of these aspects have been properly verified. Many of the studies that we have considered could be dismissed as being inadequate on at least one critical aspect. However, we have considered all relevant studies known to us, excluding only those that are generally agreed in the literature to be fatally flawed. Exclusions are detailed in the individual sections to follow.

2.2.1. CONFOUNDERS

To fulfil the first test of causality it is necessary to rule out the possibility that confounders could explain the observed association. In the studies reviewed here there is neither a consistent set of potential confounding factors nor a consistent method for adjusting for them. For most outcomes, other risk factors have been observed in independent studies which can produce relative risks at least as large

as those observed for exposure to ETS. This is supported by Lee (1994, Table 2), Thornton (1994), Katzenstein (1992), Smith et al. (1992) and others.

Diet, for example, appears to be emerging as an important confounder; it is identified in the studies of Koo (1987) and Hirayama (1984), and is discussed in detail by Lee (1992) and Byers (1994). The latter authors report some relative risks associated with dietary factors which are at least as large as that observed for exposure to ETS.

A recent public report (Mathers, 1994) finds that one of the major factors influencing health in Australia is socioeconomic status. Many of these issues are addressed in more detail in the individual sections.

2.2.2. PROBLEMS OF DEFINITION

Definition of Exposure

The definition of index of exposure to ETS varies considerably between studies with respect to source and duration. Lee (1992, Table 3.20) summarises the variety of definitions arising in various lung cancer studies. Furthermore, knowledge of cohabitation with a smoker does not necessarily imply exposure, nor is the "unexposed" group necessarily unexposed; see, for example, Friedman, Pettitti and Bawol (1983). The impact that this variation will have on the relative risk depends crucially on the shape of the true exposure-response relationship.

Multiple sources of exposure should be considered. Adults may be exposed elsewhere other than in the home (Friedman et al, 1983); children may be exposed not only to parental smoke but also to that of friends. Those studies that do report multiple sources rarely account for them adequately in the analysis. Moreover, the effects of exposure may be measured from one source and extrapolated to another source. For example, the OSHA Report (1994) analyses exposure to spousal smoking and applies the results to the workplace, ignoring the body of studies on workplace smoking.

Measurement of urinary cotinine avoids some limitations, but it measures only recent exposure. The test of temporality assumes consistency of exposure for each subject. Cotinine measurements have also been used to screen out smokers from cases who declare themselves non-smokers (e.g. see Fontham, 1994), but this may not be completely effective (Wald et al., 1984).

Time of exposure must also be considered. Definitions may be based on self-reported responses which require good recall (e.g. about exposure in childhood). Alternatively, in recording only current exposure they again fail the test of temporality. This problem is especially compounded if there are multiple exposures, for example in the evaluation of pre- and post- natal exposure.

Degree and Duration: There is debate about the adequacy of attempts to obtain continuous measures of duration and magnitude of exposure, compared with a simple unexposed/exposed categorisation. This is further exacerbated by recall bias and "surrogate" responses (see, for example, Riboli et al., 1990, and Lee, 1992 for the two sides of this argument).

The more precise categorisations of exposure are inconsistent between and even within studies. Given the comparative rarity of some of the outcomes of interest and the relatively small sample sizes, this can have substantial influence on the observed results and hence on any attributable risk calculations. Poor definition may also be reflected in different exposure-response relationships based on different measures (e.g. Akiba, 1986).

Definition of Outcome

The health outcome of interest may vary between otherwise similar studies so it is important that only comparable studies are evaluated in the assessment of a causal relationship.

An outcome should be unique. Death from heart disease is a different outcome from hospitalisation for heart disease and ischaemic heart disease differs from that due to hypertension.

An outcome should be regarded as a single entity. In many studies the outcome comprises a number of diseases (e.g. lower respiratory tract infections in childhood). Also, lung cancer encompasses a number of different histological types. As such, it is essential that diseases are precisely defined as a unit and that a relative risk for a collection of diseases is a meaningful measure.

An outcome should be a direct measure. It is difficult to assess causality if there is imprecision in the measure of *both* exposure and outcome. In the assessment of heart disease, intimal thickening is often measured, but a pathological outcome of lesions cannot be asserted without an extrapolatory step.

Outcomes determined by subject responses are also open to bias and misclassification. Responses will be influenced by the wording of questions and acquaintance with the disease. Bronchitis and wheezing are often confused by parents, even though clinically they may reflect different diseases. Adults may report asthma or bronchitis without an established clinical diagnosis; whether this differs by exposure and hence contributes to a bias is not established.

An outcome must be evaluated in the light of other outcomes. As with exposure, more than one outcome may be evaluated in a study, and it is imperative that the analysis adequately accounts for the possible correlation between responses. If not, spurious statistically significant results may be observed and important interactions between outcomes may be overlooked.

Misclassification

Misclassification of active smoking, exposure to ETS and outcome may be a result of poor definition, poor study conduct or outright misreporting by subjects.

Lee (1992) provides a review of studies which use cotinine to address this problem: the percentage of "deceivers" from the 6 papers which use cotinine validation range from 0 to 17.4%, with an overall rate of 4.3%. Wald et al. (1986) estimates misclassification of exsmokers as nonsmokers to be 4.9%. Other validation has also been attempted (see for example Humble et al., 1987; Brownson et al., 1992). Delfino et al. (1993), Jarvis et al. (1984) and McDonald et al. (1990) also found a low concordance between statements about exposure to ETS and actual exposure as measured by cotinine.

Ahlborn and Uberla (1988), Wald et al. (1986), the EPA Report (1992) and Tweedie, Mengersen and Eccleston (1994) also address this issue in the context of lung cancer; their results are discussed in Section 4.2.

Wald et al. (1986) attempts to account for this by making a single adjustment to the overall relative risk. The US EPA report (1992) attempts to be more sensitive to individual study quality by adjusting each study separately. Both methods have been criticised. In our view the paucity of data and the deficiencies in the present methods preclude rigorous assessment of and adjustment for misclassification.

There is also potential for misclassification of outcome. Death certificates are widely regarded as being potentially unreliable sources of cause of death, and not all other outcomes are rigorously established (in particular parental reports of children's diseases, and hospital records of adult health).

Respondent Bias

The problem of misclassification is exacerbated by using different respondents, including the subject and surrogates such as a spouse or child. Mengersen, Tweedie and Biggerstaff (1994) have assessed the impact of use of surrogate data on the observed association between lung cancer and exposure to spousal smoking. They conclude that, in the sixteen studies with relevant data, the use of surrogate data indeed affected study results, but not in a systematic way.

Recall Bias

The requirement to recall past exposures influences not only the misclassification rate, but can also bias the observed association if recall is different between those exposed and unexposed, or between those with and without the outcome of interest.

Kilpatrick (1986) discusses possible bias in recall of ETS exposure. Cases may recall such exposure more readily than controls, which may lead to spuriously inflated observed relative risks.

Maternal reports of children's illness has been argued to be systematically biased. In a number of case control studies mothers of case children recall more outcomes and have different hospitalisation thresholds than mothers of control children.

Publication Bias

Distortion of the overall picture of an association through publication bias has been recognised by a number of authors. Positive studies are more likely to be published than negative results. Hall (1991), in the more general context of published information on drugs, discusses two types of such bias: under-publication and over-publication. Examples of overpublication include the so-called 'Tucson Study', 'East Boston Study' and 'Six Cities Study' which have generated multiple reports; see Section 3.

Some reasons for under-publication, or selective publication, include confidentiality of results, adverse publicity, negative results, lack of time/incentive to prepare material for publication, and unwillingness on the part of some journals to accept certain studies, or nonsignificant results, for publication.

Chalmers and Buyse (1986) provide some indication of the level to which nonreporting of insignificant studies may bias overall assessment. Hall (1991) concludes (p.23) that "until the problem of inaccessible or unpublished data can be remedied, conclusions based on published information alone may be invalid."

Reporting Bias

Publication bias also exists within a paper: there is a tendency to report only the significant results. In the assessment of exposure-response, for example, Lee (1994) identifies the following problems.

- There is a tendency to report an exposure-response relationship only when it is statistically significant. Hence any overall assessment is biased towards a positive association.
- Even though such a relationship may be assessed using different indices, non-significant results may not be reported.
- There may be different confounders at different exposure levels. In the analysis of lung cancer among adults, for example, women married to heavy smokers are reported to be more exposed to confounding risk factors such as pollution, poor living conditions, etc. than women married to light smokers. Similarly, marriage concordance is reported to vary with the amount smoked, so that misclassification rates may also vary with exposure.
- The exposure-response relationship should be assessed on the exposed groups only.

Data Dredging

There are two issues which contribute to this problem:

- Hypothesis testing: a study must be designed with the goal of testing the association of interest. Early studies (hypothesis generating) and those which construct an hypothesis on the basis of the data should be viewed with caution.
- Multiple testing: Some studies report a great many comparisons, and it is impossible to assess the number of unpublished comparisons unless this is explicitly stated (see, for example, Hirayama, 1981; 1984). While such dredging may be tolerated as an exploratory tool, only results which apply to some pre-planned hypothesis should be considered as confirmatory.

- Extreme comparisons: testing should not focus on extreme groups (see, for example, Hirayama, 1981).

Wish Bias

The tendency on the part of a subject or investigator to reach a desired result is a well-recognised potential bias (Wynder et al, 1990). Self-reporting of outcomes may be affected by conscious and unconscious psychological motives and economic considerations, and this may be exacerbated by surrogate reporting. Bias on the part of investigators, through a preference to obtain positive results, is extensively covered in the literature (e.g. Hegsted, 1989). Like publication bias, however, it is difficult to evaluate the impact of this problem.

Prejudgement Bias

This applies when a study is conducted using an alternative hypothesis other than one of no association. There are two problems arising from this. The first is that the possibility of a negative (or the opposite) association is excluded. More importantly, adjustment for confounding factors may be influenced by the hypothesis. This is argued in detail by Fleiss and Gross (1991; cf Wexler, 1989, pp.154-5).

Representativeness

If the conclusions of a study are to be extrapolated to the general population then a cohort or prospective study should be as representative as possible and constructed for the purpose of testing the particular hypothesis of interest. Case control studies must also adhere to this constraint, but particular care must be taken to ensure that the controls are also representative. Misclassification and confounding effects, which may give rise to results which do not apply to the general population, should be considered. It is generally acknowledged that problems of representativeness are threefold.

The subjects used in the analysis may not be representative of the original study population. This may be through nonresponse, loss to followup, lack of information or exclusion from analysis for other reasons.

The study population may not be representative of the general population. Some populations are extreme (e.g. Gillis, 1984; Akiba et al., 1986). Hospital controls are

also widely recognised as being potentially nonrepresentative and capable of biasing the results (Hill, 1965). Other populations differ with respect to background rates of exposure (Layard, 1992; Riboli et al., 1991). Differences between populations with respect to socioeconomic status and employment may also influence the observed risk (Lew & Garfinkel, 1979; Mathers, 1994).

The study population may comprise subgroups. If the observed association is an average over particular subgroups of a population, and if inference is to be made about these subgroups, it is important that particular attention be paid to the subgroups themselves. Such differences may be explained in part by the different influences of confounders.

Other biases arise from this: under the well known Simpson's paradox, bias is introduced by collapsing contingency tables across categories, so that two subgroups may have relative risks equal to unity (so that there is no association between outcome and exposure) but when combined the overall relative risk (ignoring the subgrouping) is substantially raised. The reverse may also occur.

Statistical Methods

Scientific rigour does not rest only on the quality of the study and data collection but also relies on the quality of the statistical analysis. We are dealing here with very small effects. Even given impeccable data and study design, the following are essential:

- Statistical methods should be clearly described.
- Statistical methods should be valid.
- Statistical methods should be reproducible. This requires a complete description of how any problems are resolved (e.g. nonresponse items, outliers, choice of scales for ordinal variables, choice of cutpoints for categories).

While we recognise that there is usually a limit to journal article length and that this often forces the description of statistical analyses to be overly limited, there should at least be access to more detailed technical reports and the actual data used in the study along with the protocols for data collection, coding and analysis.

In the same way that consistency of association is required across various protocols, conclusions based on a given set of data should be consistent under a variety of assumptions (where required to overcome data quality issues) and a

variety of contemporary statistical methods. This has not been reported by authors in any individual study considered here. Furthermore, we know of no independent reanalyses of the raw data.

To illustrate this point, we identify below some instances in which choices need to be made in statistical analysis.

Study Size

Studies must be of reasonable size in order to have power to identify an effect if there is one, to guard against possible problems in study quality, and to reasonably assert representativeness. Statistical significance should be evaluated in conjunction with power: Sandler (1990) and Hole (1989) have very small numbers of cases.

Use of Approximations

Throughout this report we refer to the relative risk as the measure of interest. In retrospective case control studies this is approximated by an odds ratio; if the exposure is rare, as is the situation with lung cancer, this provides a close estimate of the desired measure (Breslow & Day, 1980; 1986). Corresponding asymptotic confidence intervals are very commonly used in the published studies. However, this may lead to spurious confidence intervals (Agresti, 1992; Mengersen, Tweedie & Biggerstaff, 1994). It is good practice to calculate exact confidence intervals whenever possible.

Multiple Testing

Because multiple tests on the same data set are not independent, each subsequent test should be more stringent.

Model Description

In many studies there is insufficient description of the methods used to analyse the data obtained. Quite often (e.g. Fontham et al, 1994) adjusted odds ratios were derived from a multiple logistic regression in which adjustments were made for various factors. Details are rarely provided on the models used and how they were actually constructed. The same list of adjusting variables is often used for different analyses without justification and with the implicit, but incorrect, assumption that one method of adjustment is applicable to all analyses.

A model may also be over-described. Hence, although exposure to ETS is a significant part of the model, the data may be quite adequately described without it.

It is also important to be cautious of inferences made on the basis of models which are constructed by excluding 'nonsignificant' factors: such inferences are conditional on these exclusions.

Exposure-Response

This is an area in which considerable inconsistencies can be observed between the various studies. First a variety of dose-response function types is biologically plausible. Possible dose response functions include:

- A step function in which there is no increased risk until a certain threshold of dose is reached, at which point there is a jump from unity to an elevated relative risk.
- Other threshold response in which once a threshold is reached the relative risk rises continuously according to some linear, quadratic, exponential or similar strictly increasing function.
- No threshold models in which risk strictly increases with every increase in dose. Possible functions here include linear, quadratic or higher power, exponential and sigmoid.

The implications of each of the above models for establishing exposure guidelines are quite different. For example, if it were established that there is a threshold effect for a dose of ETS and the threshold is estimated to exceed dose levels likely to be encountered in a variety of situations (such as the home or at work) then the epidemiological evidence would provide no motivation for restricting exposure.

Any conclusions about dose response relationships should not simply be a reflection about the type of dose response model chosen by the analyst. If a linear model is fitted to data which truly have a threshold then it is highly likely that the straight line will be judged to provide an adequate fit. However this does not prove that the dose response relationship is linear and any interpretations based on extrapolation could be quite erroneous. This applies also to attributable risk estimates based on such models.

Background Risk

Correction for 'background' exposure of the 'unexposed' groups in the ETS studies is conducted in some major reviews (e.g. EPA Report, 1992) by increasing

the derived overall relative risk estimate by a specified amount. Layard (1992) refutes the assumptions on which this 'specified amount' is based, but more importantly, emphasises that such an adjustment assumes that there is a causal relationship. Like Mantel (1990), he asserts that an evaluation of causality should be conducted before such an adjustment is made, and only then is it valid to make the adjustment.

Attributable Risk

Attributable risk computations, such as those of the EPA Report (1992), the OSHA Report (1994) and Glantz and Parmley (1991) are based on a number of assumptions.

Such assumptions should be documented explicitly and validated so that the resultant estimates reflect reality. Tweedie (1994), for example, in an open critique of the OSHA Report (1994) demonstrates that the attributable risk estimates in that document are considerably overstated when compared to Australian statistics.

Moreover, the estimates are quoted without any indication of their reliability; there is no assessment of sensitivity to changes in assumptions, nor any account taken of the amount or quality of the data on which they are based.

Meta-Analysis

A quantitative assessment of the overall association between exposure to ETS and the outcome of interest can be obtained through meta-analysis, which is a statistical technique designed to enable combination and comparison of results from studies which are comparable in outcome and exposure.

It is a useful technique to obtain some overall quantitative assessment of the association as well as identifying sources of homogeneity and heterogeneity between studies. Indeed, this can be an effective method of focusing on comparisons of studies and study quality.

There is considerable debate about the appropriateness and execution of a meta-analysis, especially with observational data. Fleiss and Gross (1991), Sacks et al. (1987), Smith et al. (1992), Feinstein (1989), Thompson (1993) Oakes (1993), Layard (1990) and Greenland and Robins (1985), among many others, provide further discussion. Important issues that must be addressed include the following:

- *Is there a possible publication bias?* If so, results should be interpreted with caution.

- *Are the results due to data dredging?* It has been argued that only results arising from pre-specified hypotheses should be included.
- *Are the study designs comparable?* This will influence the assessment of confounders and the statistical model. Meta-analysis was originally developed for randomised clinical trials over which there was strong concordance of methodology.
- *Are the studies measuring the same outcome?* If not, the results may be difficult to interpret and apply.
- *Are the study populations comparable?* Studies should only be combined on equivalent populations.
- *Is the risk constant over time?* If not, this should be explicitly taken into account in the model.
- *Are confounding factors adequately and consistently controlled?* If not, a meta-analysis should not be conducted.
- *Are the raw data subject to misclassification and bias?* A meta-analysis is not a remedy for poor quality. Models which do not take into account problems with design, misclassification or bias can reinforce these problems.
- *Are the assumptions of the meta-analysis valid?* Different statistical models can be employed in a meta-analysis (e.g. Mengersen, Tweedie & Biggerstaff, 1994; Biggerstaff, Tweedie & Mengersen, 1994). The two most common methods, based on a fixed effects and a random effects model respectively, make unrealistic assumptions. The technique employed will influence the outcome and should be explicitly described.

3. EFFECT OF ETS ON CHILD HEALTH

3.1. INTRODUCTION

Many environmental factors may contribute independently and interactively to the development of asthma in childhood (Burney, 1992; Peat et al., 1994; Seaton et al., 1994; Bjorksten et al., 1984). To date, the most important risk factors that have been identified for children having asthmatic symptoms or airway abnormalities are allergic sensitisation to common inhaled allergens such as house-dust mites, moulds, pets and pollens (Sears et al., 1993; Peat et al., 1993), a family history of asthma (Dold et al., 1992; Aberg, 1993), a serious lower respiratory tract infection in infancy (Cogswell et al., 1982, Weiss et al., 1985; Voter et al., 1988) and dietary factors (Burney et al., 1992; Pistelli et al., 1993, Seaton et al., 1994). Allergic sensitisation is the most important of these. Both breast feeding (Wright et al., 1989; Geller-Bernstein et al., 1987) and dietary fish oil (Ritter et al., 1988; Peat et al., 1992) may protect children against developing asthma.

The extent to which exposure to ETS is involved in the aetiology of asthma has not been established and the literature is reviewed below. However, the evidence which suggests that exposure to ETS is associated with an increased risk of lower respiratory tract infections in infancy also suggests that ETS is not a primary factor in asthma causation, but is more likely to be a secondary modifier for respiratory illnesses. It is also unclear whether the factor which is associated with an increased risk of respiratory infections in early childhood is exposure to ETS in infancy per se or active smoking during pregnancy, which leads to a lower birthweight and to narrower airway calibre (Bisgaard et al., 1987; Frischer et al., 1992; Kitchen et al., 1992).

In assessing the effects of ETS, it is important that accurate outcome measures are used. A major problem here is that there are no practical methods with which to measure respiratory infections or symptoms objectively. Thus, questionnaires, which can be either parent or interviewer administered, are the only tools available. Such methods are more accurate for measuring severe illness classifications such as hospitalisations or confirmed diagnoses (for which false

negative or false positive replies are less likely) than for measuring the presence or frequency of more trivial respiratory symptoms such as cough or wheeze, which may have occurred years earlier. The use of questionnaires/interviews to obtain data on past respiratory illness and symptoms in children is open to recall and reporting bias, because reporting may not be independent of the environment; for example, damp and mould in the house or socio-economic class, and other possible factors such as respiratory illness and symptoms exhibited by the child, or awareness by parents of potentially adverse environmental circumstances, could influence parents' responses.

Concerns about study quality as outlined in Section 2.2 of this report are relevant to the studies included in our assessment of the literature dealing with the health of children and ETS. Rarely is a study without at least some flaws; however, we have considered about 200 epidemiological studies which we feel are representative of the current literature. In sections 3.2.1 - 3.2.5, cross-sectional, case-control and cohort studies which have examined the effect of ETS on lower respiratory tract infections and on wheeze, asthma and allergy in infants and children are reviewed. Studies which have been omitted are those which have enrolled only hospital or tertiary referral patients and those which have not enrolled an appropriate control group so that no general conclusions about the effects of ETS can be drawn and those studies based on very small samples. Further, the accompanying tables 3.2.1 - 3.2.4 contain both unadjusted and (wherever possible) adjusted odds ratios or relative risk ratios. Since the impact of confounders can be substantial, the unadjusted results should be viewed with caution.

3.2. Lower Respiratory Symptoms and Illness

3.2.1 Lower Respiratory Tract Infections in Infants

No standardised methods have been established for measuring lower respiratory tract infections in young infants. In general, the data which have been recorded include bronchitis, pneumonia and other non-specific viral and bacterial infections, usually requiring treatment by a doctor or admission to a hospital. There is evidence that such infections in early life, that are serious enough to require medical consultation, are important risk factors for later development of airway hyper-responsiveness (AHR) (Weiss et al., 1980; Voter et al., 1988; Peat et al., 1992) but the issue of whether they are the first manifestation of asthma or whether the resultant inflammation predisposes to later asthma has not been resolved.

Infants exposed to ETS are more likely than those unexposed to be hospitalised for a lower respiratory tract infection. The study with the largest sample size found an *unadjusted* odds ratio for hospitalisation for 'bronchitis, bronchiolitis, pneumonia or wheezing' of 2.0 (95% CI 1.5,2.8) (Taylor et al., 1987) and other studies report similar findings, see Table 3.2.1. The studies conducted in China, where few women smoke, have been important because any measured effect of ETS is largely independent of *in utero* exposure. Studies conducted in Shanghai found an unadjusted risk ratio for children aged 1-6 months exposed to ETS of 2.7 (95% CI 1.5,5.0) for being hospitalised for respiratory disease (as defined by ICD codes), while for children aged 7-18 months this was reduced to 1.6 (95% CI 0.9,2.9) (Chen et al., 1988), but in a later study no significant results were reported (Chen et al., 1989). Boys who had a low birthweight, or who were not breast-fed, were at greater risk.

Studies from other countries report similar findings for the incidence of bronchitis, bronchiolitis and pneumonia with unadjusted odds ratios which range from 1.4 (95% CI 1.0,2.0) to 3.2 (95% CI 1.4,7.3) (Leeder et al., 1976b; Rylander et al., 1993; Pedriera et al., 1985; Colley et al., 1974; McConnachie et al., 1986a). These odds ratios are not adjusted for confounders which may alter the estimates. For example, Colley et al. (1974) found an unadjusted odds ratio of 2.5 (95% CI 1.6, 3.9) for the risk of respiratory infection in the child's first year if both parents

smoked, which reduced to 2.3 (95% CI 1.4, 3.6) when a single confounder, parental history of cough, was taken into account (allowing for other confounders could further reduce the odds ratio).

The risk of infants having non-specific lower respiratory tract infections in the presence of ETS is lower. However, the criteria used to define non-specific lower respiratory tract infections have varied widely. Outcome variables that have been used include a summative score for respiratory illness (Woodward et al., 1990), a lower respiratory tract illness confirmed by a physician according to pre-determined criteria (Martinez et al., 1988a, Wright et al., 1991), a respiratory tract infection recorded by a health visitor (Ogston et al., 1987), a wheezy chest including bronchitis, bronchiolitis and pneumonia (Fergusson et al., 1980; Fergusson et al., 1981; Forastiere et al., 1992), and prolonged colds for more than two weeks (Burr et al., 1989). One study found no effect on cough in infancy (Schenker et al., 1983). Some of these studies have adjusted for other confounding variables. In addition, some studies appear to have demonstrated a dose-response effect of ETS but only with respect to *unadjusted* rates (Colley et al., 1974; Fergusson et al., 1981; Chen et al., 1986; Chen et al., 1988). A study of children with a family history of atopy (Burr et al., 1989) found a risk similar in magnitude to other studies which have enrolled random samples of children. This suggests that atopic children are not at greater risk of serious respiratory tract infections if exposed to ETS than non-atopic children.

3.2.2 Lower Respiratory Tract Infections in Children

The effect of ETS on lower respiratory tract infections in children of school age is less certain, Table 3.2.2. Although some researchers find a non-significant or a small association between ETS and recent cough reported by parents (Weiss et al., 1980; Lebowitz et al., 1976; Forastiere et al., 1992; Park et al., 1986; Andrae et al., 1988; Somerville et al., 1988), some others find a stronger relation in older children who report their own symptoms (Charlton, 1984). However, in this last study, the only symptom to have a significantly increased risk was "a lot of coughs". The risk measured may have been affected by measurement error and perception in questionnaires answered by a surrogate (usually the mother). When salivary cotinine levels were used as a marker, the frequency of recent chest colds in 6-7 year olds was increased in exposed subjects with an odds ratio of 1.1 (95% CI 1.0, 1.3) (Strachan et al., 1990). However, exposure was not an important determinant of wheeze, cough and sore throat.

3.2.3 WHEEZE IN INFANCY

Although wheeze in infancy is often the first indication that asthma may develop at a later age, some wheeze may be entirely due to smaller airway diameter rather than to abnormal airway pathology. Children who have low birthweight or who are male are more likely to have smaller airways and to develop allergic sensitisation in early childhood, are at increased risk for having reduced airway calibre (Frischer et al., 1992; Kitchen et al., 1992; Martinez et al., 1988b) and are at a greater risk for having wheeze associated with exposure to ETS (Bisgaard et al., 1987; Rylander et al., 1993; Halken et al., 1991) (Table 3.2.3), although Schenker et al. (1983) found no effect. Children with an atopic family history are at increased risk for developing wheeze if exposed to ETS (Burr et al., 1989).

3.2.4 WHEEZE IN CHILDREN

In children of school age, exposure to ETS was reported to be associated with increased frequency of current episodes of wheezing (Somerville et al., 1988; Chan et al., 1989; McConnachie et al., 1989) and of night cough (Strachan et al., 1988). Burchfiel et al. (1986) reported an excess of wheeze, asthma and chest colds in children of smoking parents but assumed that all children under 15 years old were non-smokers. Only 126 out of 4378 16-19 year olds admitted smoking, a rate much lower than might be expected. Ekwo et al. (1983) reported an increased prevalence of cough and colds with exposure, but not dyspnoea, wheeze or sputum (see also, Neuspeil, 1989). Other studies reported no significant increase in the risk of wheeze with exposure to ETS, (Schenker et al., 1983; McConnochie et al., 1986b; Lebowitz et al., 1976; Toyoshima et al., 1987; Tsimoyanis et al., 1987 and Rylander et al., 1988).

3.2.5 ASTHMA

Allergy

In most children asthma is associated with sensitisation to common allergens. Thus, it is important to establish whether exposure to ETS increases the risk of childhood asthma by increasing the risk of children becoming sensitised. One study found that infants whose mothers smoke have a cord IgE level at birth that was, on average, double the expected value (Magnussen, 1986), but a study in Australia failed to confirm this association (Young et al., 1991). Although IgE

mediated responses are an important feature of asthma (Burrows et al., 1989; Sears et al., 1991), there is no evidence to suggest cord IgE levels at birth may lead to later allergic sensitisation and asthma.

Studies of older children that have used objective outcome measurements of skin prick tests and IgE levels, show that exposure to ETS is associated with an increase in the risk of being sensitised. In the USA, a study of 12-16 year olds found that children exposed to ETS were at increased risk of becoming sensitised to common allergens (Weiss et al., 1985) and, in Italy, a study of 9 year olds found that exposure to ETS was associated with increased IgE levels (Ronchetti et al., 1990) and degree of sensitisation (Martinez et al., 1988; Palmieri et al., 1990). Airway inflammation as a result of respiratory infection may facilitate allergens crossing the epithelium of the airways to enable sensitisation and, because boys exhibit higher rates of sensitisation than girls in childhood (Peat et al., 1992; Sears et al., 1993), it has been suggested that they may be more susceptible to the effects of ETS.

Asthma in infancy

Wheeze is a frequent symptom in infants but only a small percent of children who wheeze before the age of 3 years go on to have reduced lung function and clinically important asthma (Martinez et al., 1988b). Thus, the presence of asthma in infants is difficult to diagnose with accuracy. Of the six studies which have classified asthma in infants as an 'allergic disorder', or by a direct questionnaire response to 'asthma' or repeated episodes of wheeze, four have found no influence of ETS (Horwood et al., 1985; Chen et al., 1988; Schenker et al., 1983 and Dodge, 1982) and the remainder have found an increase in risk of asthma if the infant is exposed to ETS (Weitzman et al., 1990; Magnussen, 1986; Arshad et al., 1992; Arshad et al., 1993) (Table 3.2.4).

Asthma in childhood

Several studies have reported that exposure to ETS is associated with an increased incidence (Sherman et al., 1990) or prevalence (Martinez et al., 1992; Stern et al., 1989; Weiss et al., 1985; Gortmaker et al., 1982) of childhood asthma and that ETS may trigger acute exacerbations in asthmatic children (Chilmoncyzk et al., 1993). On the other hand, a number of studies found no significant association between

exposure to ETS and asthma (O'Connel & Logan, 1974; Leeder et al., 1976b; Dodge, 1982; Schenker et al., 1983; Horwood et al., 1985 and Chen et al., 1988).

Airway hyper-reactivity (AHR) is an objective marker of airway abnormality associated with asthma and is measured by pharmacological challenge, exercise, cold air or bronchodilator response. However, because repeated compliance with forced expiratory manoeuvres is difficult to obtain from children below 8 years of age, this measurement is only useful for assessing airway abnormality in older children. The response to carbachol was found to be significantly higher in male children exposed to ETS and a dose-response effect was demonstrated in boys with an odds ratio of 4.2 (95% CI 1.4,12.9), but not in girls, with an odds ratio of 1.5 (95% CI 0.6,3.8) (Martinez et al., 1988a).

A study which found that changes in airway calibre (FEF_{25-75}) post bronchodilator were 4% higher in children exposed to ETS suggested that children exposed to ETS may have more reactive airways than those not exposed (Ekwo et al., 1983). However, exposed children did not have a higher prevalence of wheeze or dyspnoea. In an Australian study, exposure to ETS had no effect on AHR to histamine after lower respiratory tract infection in early childhood had been taken into account (Peat et al., 1992). This suggests that the association between ETS and respiratory infections in early life may account for the subsequent association with AHR.

3.2.6 Consistency

Although the odds ratios/risk ratios for respiratory infections, wheeze and diagnosed asthma are small, estimation of their magnitude has been fairly consistent across some studies; nevertheless caution must be exercised because confounders may account for much of the association and a number of studies have failed to show any significant effects. Studies which have measured severe conditions, such as hospitalisations or diagnosed infections, show with reasonable consistency that exposure to ETS increases the risk of infections in infancy. There is some evidence that some subgroups (low birthweight infants, especially boys, atopic children and babies who are not breastfed) may be at increased risk from the effects of ETS. Results regarding older children are inconsistent and indeed any effects appear to dissipate with age (e.g. Colley et al., 1974). Alternatively, these associations may reflect the influence of smoking during pregnancy.

3.2.7 Confounders

Because ETS is not the only factor which is involved either directly or indirectly in the aetiology of asthma, it is important that other factors (confounders) are taken into account. When the effect of ETS is estimated using multivariate models, the association with respiratory illness or symptoms is generally reduced (see Tables 3.2.1 to 3.2.4).

The most important risk factor for childhood asthma is sensitisation to common allergens (Sears et al., 1993; Peat et al., 1993) and many other factors related to housing conditions may be surrogates for allergen exposure. Strachan (1988) showed that the odds ratio between mould visible in the home and wheeze, adjusted for housing tenure, number of smokers in the household, number of people per room and gas cooking, was 3.0 (95% CI 1.7,5.3). In addition, both genetic factors and age are important in the development of asthma. Several of the reviewed studies show that children of parents with a history of asthma or bronchitis have increased rates of respiratory illness (Colley et al., 1974; Ekwo et al., 1983; Burchfiel et al., 1986; Pedreira et al., 1985; Ferris et al., 1985) and other studies show an association between age and wheeze (Martinez et al., 1988b; Peat et al., 1992). Charlton (1984) found that the risk ratio for frequent cough changed from 1.6 (95% CI 1.3,2.0) for girls under 11 years old to 1.0 (95% CI 0.6,1.6) for boys older than 14 years.

Socio-economic status (SES) is another important factor in the aetiology of asthma. There is evidence that children of parents with a low SES or with a less 'westernised' lifestyle are less susceptible to allergic respiratory illnesses but are at greater risk of serious respiratory tract infections such as bronchitis (Veale et al., 1991; von Mutius et al., 1993), whereas children with a high SES or a more 'westernised' lifestyle are at greater risk for allergic disorders, including asthma (von Mutius et al., 1993; Burney, 1992). Although SES is rarely taken into consideration, Schenker et al. (1983) reported that SES had a significant effect on symptoms and Bisgaard et al. (1987), showed that the odds ratio for wheeze associated with SES, went from 2.2 for SES class 0-4 down to 0.7 for SES class 13. Martinez et al. (1992) showed that there was no association between maternal smoking and the incidence of asthma in children of mothers with more than 12 years education.

Other important confounders for allergic and respiratory disorders in early childhood are low birthweight, which is associated with smaller lungs and consequently with narrow airway calibre (Frischer et al., 1992; Kitchen et al.,

1992), regular daycare, which increases rates of lower respiratory tract infections and early wheeze (Bisgaard et al., 1987), and breastfeeding which protects against early respiratory illness (Wright et al., 1989a; Geller-Bernstein et al., 1987).

3.2.8 CONCLUDING REMARKS ON LOWER RESPIRATORY ILLNESS

Although the results are not entirely consistent, it can be inferred that exposure to ETS is associated with an increased risk of lower respiratory tract infections in infants, but causation as defined earlier has not been demonstrated. ETS is unlikely to be a primary factor in asthma causation, but may be a secondary modifier for respiratory illnesses. Other confounders may also be important risk factors. It is unclear whether the important factor is exposure to ETS in infancy *per se* or active smoking during pregnancy, which leads to a lower birthweight and to narrower airway calibre. The situation with respect to older children is unresolved.

Table 3.2.1
Summary of effects of ETS on lower respiratory tract infections in infants

Author	Journal	Year	Country	Age	N	Outcome	Unadj. OR/RR	Adj. OR/RR
Taylor *et al*	Arch Dis Child	1987	UK	0-5	12727	Hospitalised	2.0 (1.5,2.8)	unavailable
Stern *et al*	Environ Int	1989	Canada	<2	4099	Hospitalised	1.9 (1.5,2.2)	1.0 (0.7,1.4)
Chen *et al*	BMJ	1986	China	1-2	1066	Hospitalised	1.1 (0.6,2.1);1-9cigs/day 1.9 (1.1,3.3);10+cigs/day	1.2 (0.6,2.4);1-9cigs/day 1.9 (1.1,3.4);10+cigs/day
Chen *et al*	Int J Epid	1988	China	0-2	2227	Hospitalised	1.6 (1.0,2.4);1-19cigs/day 2.1 (1.4,3.2);19+cigs/day	1.7 (1.1,2.6);1-19cigs/day 2.2 (1.5,3.4);19+cigs/day
Fergusson *et al*	Arch Dis Child	1980	NZ	1 yr	1180	Hospitalised	4.5 (1.8,10.2)	unavailable
Leeder *et al*	Br J Prev Soc M	1976	UK	1 yr	1959	Bronchitis/pneumonia	2.6 (1.8,3.8)	2.5 (1.4,4.3)
Rylander *et al*	Eur J Epid	1993	Sweden	0-4	550	Bronchitis	2.6 (1.4,4.8)	1.8 (0.9,3.8)
Pedniera *et al*	Pediatrics	1985	USA	1 yr	1144	Bronchitis	1.4 (1.0,2.0)	unavailable
Colley *et al*	Lancet	1974	UK	1 yr	2205	Bronchitis/pneumonia	2.5 (1.6,3.9)	2.3 (1.4,3.6);only one confounder
McConnachie *et al*	Am J Dis Child	1986	USA	2 yr	159	Bronchiolitis	3.2 (1.4,7.3)	1.4 (1.1,1.8)
Forastiere *et al*	Int J Epid	1992	Italy	2 yr	2929	Bronchitis/pneumonia	1.3 (1.0,1.6)	0.9 (0.6,1.3)
Woodward *et al*	JECH	1990	Australia	1-3	489	LRI	2.4 (1.6,3.6)	0.8 (0.4,1.7);breastfed
Martinez *et al*	NEJM	1988	USA	1 yr	124	LRI	unavailable	1.3 (0.4,3.9)
Ogston *et al*	JECH	1987	UK	0-1	1910	LRI	1.7 (1.3,2.4)	1.5 (1.2,2.1)
Fergusson *et al*	Ped Pul.	1985	NZ	0-2	1115	LRI	1.5 (1.1,2.2)	1.1 (1.0,1.3)
Fergusson *et al*	Arch Dis Child	1980	NZ	1 yr	1180	LRI	1.6 (1.3,2.1)	unavailable
Wright *et al*	J Pediatrics	1991	USA	1 yr	1246	LRI	1.8 (1.1,2.9)	1.2 (0.6,2.3);daycare
Burr *et al*	JECH	1989	UK	1 yr	481	LRI	unavailable	1.6 (1.1,2.5)

Table 3.2.2
Summary of effects of ETS on lower respiratory tract infections in children

Author	Journal	Year	Country	Age	N	Outcome	Unadj. OR/RR	Adj OR/RR
Charlton	BMJ	1984	UK	8-19	15709	Frequent cough	1.5 (1.3,1.6)	1.0 (0.7,1.5):boys≥14yrs 1.6 (1.3,2.0):girls<11yrs
Park *et al*	Yonsei Med J	1986	Korea	0-14	3651	Recent cough	1.9 (1.3,2.9)	1.7 (1.2,2.2)
Andrae *et al*	Arch Dis Child	1988	Sweden	0-16	4990	Prolonged cough	unavailable	1.3 (1.1,1.6)
Somerville *et al*	JECH	1988	UK	5-11	5103	Cough	1.5 (1.3,1.8)	1.3 (1.1,1.6):20cigs/day
Forastiere *et al*	Int J Epid	1992	Italy	7-11	2929	Chest illness	1.0 (0.9,1.2)	1.0 (0.7, 1.3)
Strachan *et al*	Am Rev Resp Dis	1990	UK	6-7	770	Chest colds	1.1 (1.0,1.3)	unavailable

Table 3.2.3
Summary of effects of ETS on the presence of wheeze in infants and children

Author	Journal	Year	Country	Age	N	Outcome	Unadj OR/RR	Adj OR/RR
Infants								
Bisgaard *et al*	Acta Ped Scand	1986	Denmark	1 yr	5923	Wheeze at 1 yr	2.7 (1.8,4.0)	unavailable
Martinez *et al*	New Eng J Med	1988	USA	1 yr	124	LRI with wheeze	unavailable	1.3 (0.4,3.9)
Rylander *et al*	Eur J Epid	1993	Sweden	0-4	550	Severe wheeze	2.6 (1.4,4.8):≤18mons	1.5 (0.7,3.2):>18 mons
Halken *et al*	Allergy	1991	Denmark	1 yr	276	Recurrent wheeze	2.4 (1.2,3.9)	unavailable
Burr *et al*	J Epi Comm Health	1989	UK	1 yr	519	Wheeze	2.5 (1.6,3.8)	1.61(1.0,2.5)
Children								
Ekwo *et al*	Chest	1983	USA	6-12	1138	Wheeze with colds	1.3 (1.0,1.8)	unavailable
Somerville *et al*	J Epi Comm Health	1988	UK	5-11	5103	Wheeze most days	1.8 (1.3,2.3)	1.6 (1.2,2.2):20cigs/day
Strachan *et al*	BMJ	1988	UK	6-7	881	Night cough	2.2 (1.4,3.3)	ETS confounder only in study of mould
Neuspiel *et al*	Am J Pub Health	1989	UK	0-10	9670	Wheezy bronchitis	1.4 (1.2,1.7)	1.3 (1.0,1.7):1-4cigs/day 1.5 (0.9,2.6):>24cigs/day
Chan *et al*	Arch Dis Child	1989	UK	7	221	Wheeze	1.7 (0.7,4.2):reference set 2.9 (1.2,6.8):low birthwt	3.4 (1.1,10.2):low birthwt
Burchfiel *et al*	Am Rev Resp Dis	1986	USA	0-19	3482	Wheeze	unavailable	1.5 (1.1,2.0):males 1.6 (1.2,2.1):females
McConnachie *et al*	Ped Pulmonology	1989	USA	13	153	Wheeze	2.5 (1.2,5.3)	unavailable
Allergy								
Weiss *et al*	Am Rev Resp Dis	1985	USA	12-16	137	Skin prick tests	2.2: P-value<0.02	unavailable
Ronchetti *et al*	J Allergy Clin Imm	1990	Italy	9	159	Serum eosinophils	6.1 (0.7,25.3)	unavailable
Martinez *et al*	Am Rev Respir Dis	1988	Italy	9	166	Skin prick tests	R=0.3, P<0.01	unavailable
Palmieri *et al*	Eur J Pediatr	1990	Italy	1-2	735	Skin prick tests	some significant effects: age < 6 yrs	unavailable

Table 3.2.1
Summary of effects of ETS on the presence of asthma in infants and children

Author	Journal	Year	Country	Age	N	Outcome	Unadj ORRR	Adj OR
Infants								
Weitzman *et al*	Pediatrics	1990	USA	0-5	4331	Diagnosed asthma	2.1 (1.3,3.4)	2.1 (1.2,3.7)
Magnussen *et al*	J Allergy Clin Imm	1986	Sweden	1-2	190	Certain asthma	2.7 (1.0,7.7)	unavailable
Chen *et al*	Int J Epid	1988	China	0-2	2227	Asthma	1.3 (0.7,2.2)	unavailable
Arshad *et al*	Lancet	1992	UK	1 yr	1167	Asthma	2.3 (1.3,3.9)	unavailable
Arshad *et al*	Clin Exp Allergy	1993	UK	2 yrs	1172	Asthma	unavailable	2.2 (1.5,3.4)
Stern *et al*	Environ Int	1989	Canada	<2	4099	Asthma	1.4 (1.1,1.9)	1.0 (0.7,1.4)
Children								
Gortmaker *et al*	Am J Pub Health	1982	USA	0-17	3072	'Impairing' asthma	2.0 (P-value<0.01)	2.3 (P-value=0.13)
Sherman *et al*	Am J Epid	1990	USA	5-9	770	Incidence of asthma	unavailable	1.2 (0.8,1.8)
Martinez *et al*	Pediatrics	1992	USA	5-12	665	New diagnosis asthma	1.7 (1.1,2.6)	1.6 (1.0,2.4)
Chilmonczyk *et al*	New Engl J Med	1993	USA	1-13	199	Exacerbations	1.8 (1.4,2.2)	unavailable
Shenker *et al*	Am Rev Respir Dis	1983	USA	5-14	4070	Diagnosed asthma		No sig. effect: multi log regn
AHR								
Ekwo *et al*	Chest	1983	USA	6-12	1138	BD response		FEF_{25-75} 4% higher: not significant
O'Connor *et al*	Am Rev Respir Dis	1987	USA	6-21	286	AHR (cold air)		some sign results
Peat *et al*	Eur Respir J	1992	Australia	8-12	1216	AHR (histamine)		No effect above ERI
Martinez *et al*	Am Rev Respir Dis	1988	Italy	9	166	AHR (carbachol)	4.2 (1.4,12.9) males	unavailable
Forastiere *et al*	Am J Resp CC Med	1994	Italy	7-11	1183	AHR (methacholine)	unavailable	2.8 (0.6,12.8):boys, overcrowding & maternal smoking

3.3. LUNG FUNCTION IN CHILDREN

Forty six papers on lung function in children form the basis of this report (Table 3.3.1); these papers are included in the References. All but four of the studies deal with children of school age or older. This is to be expected, given the difficulties that children have in performing respiratory manoeuvres for spirometric tests. However, some studies include children under 7 or 8 years old. As a consequence of these difficulties and the variability of the measurements, the data analysed are typically the 'best' of three or five tests or the average of the 'best' three or five tests.

The most common lung function data obtained were Forced Vital Capacity (FVC) measurements which were used to derive FEV_1 or, in some studies, $FEV_{0.75}$ (forced expiratory volume in one 1.0 or 0.75 second) and FEF_{25-75} (airflow between 25% and 75% of FVC) and, to a lesser extent, $Vmax_{50}$ (airflow at 50% of FVC). Other values were derived and used occasionally, but in fact so rarely that no worthwhile conclusions could be inferred. Our comments are for the most part in regard to FEV_1, FEF_{25-75} and, to a lesser extent, FVC and $Vmax_{50}$.

Before commenting on the results of the studies a few points need to be made. There are no perfect studies to date. Indeed some of those reviewed in this section are seriously flawed; their limitations are discussed later in the section. Clearly, if the sample or subjects are not randomly selected, or are not representative of any particular population, then inferring conclusions to a broader group than those studied is questionable. Also, non-response, refusal to participate, as well as the withdrawal of subjects during a study may bias the results. The measurement of exposure to ETS varied greatly between the studies; the most common indices were maternal smoking only, paternal smoking only, both parents smoking, number of cigarettes per day, and heavy smoker versus light smoker. In addition, current smoking status of parents is used frequently as a surrogate for past exposure to ETS. Location (that is, country of study, rural or urban, suburban or industrial) is a variable that may have an effect due to different exposures, different cultures and customs, availability of medical help and other social factors. The almost universal use of questionnaires/interviews to obtain data on

past respiratory illness and symptoms of children is open to recall and reporting bias.

There is considerable variation in the results of the studies which could be due to study design, sampling strategies such as selective sampling, statistical methods, measurement of exposure to ETS, reporting biases, recall bias, and small sample size; studies with such flaws are noted in Table 3.3.1. Also, definitions of disease and the effects of various confounders, including ETS, the source of which is usually parental smoking (almost always maternal), can result in variation between studies. Some of the studies do not consider socio-economic status of the parents as a factor; this is known to be an important indicator of poor health and high risk lifestyle (Mathers, 1994).

In many studies ETS is not the most important risk factor in terms of magnitude or statistical significance. In fact, when multivariate analyses are used which incorporate many of the above-mentioned factors, passive smoking can be shown not to be a significant factor, as is exemplified in the details of the results of the studies given below.

In general, all the lung function measurements were adjusted for age, height and sex, and sometimes weight. These factors appear to account for much of the variation in lung function. For the studies of school children, FEV_1 (or percent predicted) was reported significantly reduced in 21 studies; these are indicated in Table 3.3.1. The reported (significant) reductions in lung function were variable, but were generally small. Ware et al. (1984) reported an FEV_1 reduction of less than 1%, Forastiere et al. (1994) reported 1.6% and Burchfiel et al. (1986), reported about 5%. Significant reductions were also reported by Yarnell et al. (1979), but for heavy smokers only, and Chen et al. (1986b) for girls only. FVC was reported to have changed significantly in 11 studies (see Table 3.3.1); once again the changes were small.

A reduction in FEF_{25-75} was reported in 15 studies (see Table 3.3.1), but again the results were mixed; Rona et al. (1993) and Martinez et al. (1992) were for boys only, Tashkin et al. (1984) for girls 12 years or older only, and Vedal et al. (1984) for girls only. Change in $FEF_{50}/Vmax_{50}$ was reported to be significant in 3 studies. Similar to the FEV_1 results, the magnitude of the changes in FEF_{25-75} and $FEF_{50}/Vmax_{50}$ were generally small but more variable; for example, Forastiere et al. (1994) reported 3.6% and Martinez et al. (1992) reported 10% for boys.

Almost all of the significant results relate to maternal smoking.

Numerous tests were often performed on the same data; this affects the overall 'p-value', and many of the tests are not independent. For example, Strachan et al. (1990) considered 12 measures of pulmonary function most of which were dependent.

Generally speaking, any observed effects seem to disappear or at least dissipate with age. The possibility of active smoking is of concern with older children. Further, some results do appear to vary with age between the sexes; for example, Tashkin et al. (1984) reported that only young (<12 years old) males had significantly reduced lung function, while only older (≥12 years old) females had significantly reduced lung function.

Other risk factors were significant and may account for much of any observed effect. The history of the child's respiratory illness or symptoms was reported by Berkey et al. (1986) to be significantly associated with lower FEV_1; potential risk factors like this are often not considered in a study. Similarly, Martinez et al. (1992) showed that maternal education is an important confounding effect and is independent of maternal smoking; many such confounders or alternative risk factors are related to socio-economic status.

A number of studies were longitudinal and formed a specific 'set'; in particular, the 'Tucson Study' (Lebowitz et al., 1982; 1984a,b; 1987a,b; Martinez et al., 1992), which reported very few significant results due to ETS, while the 'East Boston Studies' (Tager et al., 1976; 1979; 1983; O'Connor et al., 1987; Sherman et al., 1990; Weiss et al., 1980) and the 'Six Cities Study' (Berkey et al., 1986; Ferris et al., 1985; Ware et al., 1994; Speizer et al., 1980), reported some significant results. The differences between these studies could be partially explained by variations in climate, geography and population mixes.

Studies by Tager et al. (1993), Hanrahan et al. (1992), Stern et al. (1989) and Cunningham et al. (1994) consider the effects of pre- and/or post-natal exposure to ETS (essentially maternal smoking) in very young children. Smoking during pregnancy and early occurrence of wheeze were shown to have a significant effect on lung function in Tager et al. (1993). Hanrahan et al. (1992) showed that no differences in pulmonary function were evident among infants exposed and unexposed to ETS in the home, after allowing for pre-natal exposure. Stern et al. (1989) estimated a decrement in FEV_1 of 1% due to smoking during pregnancy

and of 0.7% with smoking exposure in the first 2 years of life, and observed no effect on FVC. Cunningham et al. (1994) reported that after adjusting for maternal smoking during pregnancy, current maternal smoking status was not associated with a significant decrease in any lung function measure. Smoking during pregnancy is revealed to be an important risk factor in most studies, but it is difficult to account for especially since it is commonly assumed that mothers who smoke during pregnancy continue to do so after the birth.

In conclusion, the studies to date display a mixed set of results, with some inconsistencies, concerning the effects of ETS on lung function in children. Generally, the effects are small and of the same order as the variation observed in duplicate testing of individuals (see, for example, Dijkstra et al., 1990). Also, the potential for confounders to account for much of any observed differences cannot be ignored.

Table 3.3.1 *Lung function studies*

Authors	*Effect*	*Author*	*Effect*
Rona et al. (1993)	c*	Hasselblad et al. (1981)	a
Spinaci et al. (1985)	a	Lebowitz et al. (1984b)	
Teculescu et al. (1986)	a	Tager et al. (1983)	a, c
Guesner et al. (1994)	a, b, c	Tashkin et al. (1984)	c*
Yarnell et al. (1979)	a, c	Vedal et al. (1984)	b, c*
Tager et al. (1976)	a	Lebowitz et al. (1987b)	b
Lebowitz et al. (1982)		Kauffmann et al. (1989)	a, b, c
Lebowitz et al. (1984a)		Chan et al. (1989b)+	
Lebowitz et al. (1987a)		Dijkstra et al. (1990)+	a
Murray et al. (1986)+	a, c	Strachan et al. (1990)	c
Cook et al. (1993)	a, b	Ware et al. (1984)	a
Casale et al. (1991)	b	Leeder et al. (1976a)	
Forastiere et al. (1994)	a, c	Chen et al. (1986b)+	a*
Burchfeil et al. (1986)	a, b	Tager et al. (1979)	
Evans et al. (1987)		Weiss et al. (1980)	c
Murray et al. (1989)+	a, c	Tsimoyianis et al. (1987)+	
O'Connor et al. (1987)	a, b, c	Schilling et al. (1977)+	
Sherman et al. (1990)+		Speizer et al. (1980)	b
Oldigs et al. (1991)+		Dodge (1982)+	a
Martinez et al. (1992)+	b*, c*	Tager et al. (1993)	
Berkey et al. (1986)	a	Hanrahan et al. (1992)	
Ekwo et al. (1983)+	a, c	Stern et al. (1989)	
Ferris et al. (1985)	a, b	Cunningham et al. (1994)	

Significant reductions are coded as: a = FEV_1, b = FVC, c = FEF_{25-75}.

Studies with notable design flaws are indicated by +

An * indicates significant results for girls only or boys only.

3.4. Upper Respiratory Tract Infection

A wide variety of outcomes are considered to indicate Upper Respiratory Illness (URI) in children, including otitis media (OM): (Teele et al., 1989; Takasaka, 1990), OM with effusion (Hinton, 1989; Barr & Coatesworth, 1991), recurrent OM (Tainio et al., 1988; Rowe-Jones & Brookbank, 1992), acute OM (Pukander et al., 1985), middle ear infection (Flemming et al., 1987), middle ear effusion (Kraemer et al., 1983; Iverson et al., 1985; Reed & Lutz, 1988; Strachan et al., 1989; Etzel et al., 1992), tonsillectomy and adenoidectomy (Said et al., 1978), glue ear (Black, 1985), sore throats (Willatt, 1986) and snoring (Corbo et al., 1989).

Many of these papers have such serious flaws with regard to the study design and/or analytical methodology, that we consider their conclusions to be equivocal at best.

Problems include:

- Highly selective sampling, so that it is impossible to judge how representative the sample is (Iverson et al., 1985; Willatt, 1986; Reed & Lutz, 1988; Corbo et al., 1989; Hinton, 1989; Etzel et al., 1992).
- Recall bias from retrospective questions or surrogate respondents (Said et al., 1978; Willatt, 1986; Reed & Lutz, 1988).
- Poor analytical methodology (such as no multivariate analyses or logistic regressions) (Kraemer et al., 1983; Willatt, 1986; Reed & Lutz, 1988; Hinton, 1989; Etzel et al., 1992).
- Low response rate - 45% in the case of Read and Lutz (1988).
- No serious attempt to allow for confounders such as socio-economic class, or parental/sibling history of disease (Said et al., 1978; Kraemer et al., 1983; Iverson et al., 1985; Corbo et al., 1989; Hinton, 1989).
- Poorly presented results with no data or summary tables (Takasaka, 1990).
- Data adequately explained without reference to passive smoking factors (Iverson et al., 1985; Corbo et al., 1989).
- Bias from aims of the study being made known to the participating children/parents (Barr & Coatesworth, 1991). Incidentally this last paper reports no significant effects of passive smoking.

Although parental smoking was determined to have a deleterious effect on chronic middle ear disease in univariate analyses (those not allowing for possible confounding effects) in Black (1985), Pukander et al. (1985), Flemming et al. (1987), Tainio et al. (1988), Strachan et al. (1989), and Teele et al. (1989), multivariate analyses (those allowing for confounders) revealed no significant effects of passive smoking (Flemming et al., 1987; Tainio et al., 1988; Teele et al., 1989), or a marginally significant effect of passive smoking (Black, 1985; Strachan et al., 1989).

However, significant effects included:

- day-care attendance (Black, 1985; Flemming et al., 1987; Tainio et al., 1988);
- child's age (Flemming et al., 1987; Teele et al., 1989);
- crowding among younger children (Flemming et al., 1987; Tainio et al., 1988);
- occurrence of child's own atopic disease (Tainio et al., 1988);
- child's gender (Teele et al., 1989);
- sibling history of ear infection (Black, 1985; Teele et al., 1989);
- breastfeeding (Teele et al., 1989);
- working mother with non-manual working father (Black, 1985);
- unsealed home heating (Black, 1985);
- older sibling only (Black, 1985);
- being born in Oxfordshire (Black, 1985).

No multivariate analyses were carried out by Pukander et al. (1985). Rowe-Jones and Brookbank (1992) found no significant associations between passive smoking and ear grommet insertion, sibling history of tympanostomy tube insertion, tonsillectomy or adenoidectomy.

Overall, passive smoking, if it has a deleterious effect on middle ear disease, results in only a small increase in risk, is not the only risk factor and is probably not the most important. Other factors, such as day-care attendance and crowding, appear more important. In Flemming et al. (1987) the odds ratio for day-care attendance was 3.2 (95% C.I. 1.4, 7.2) and for crowding 3.4 (95% C.I. 1.3, 8.6),